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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SNYDER, STUART	
ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,498	ZHANG ET AL.	
	Examiner	Art Unit	
	STUART W. SNYDER	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,8 and 10-56* is/are pending in the application.

4a) Of the above claim(s) *3,4 and 34-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2,10-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Amendment to claims 1 and 23 in Applicants' filing of 11/11/2008 is acknowledged. Claims 1, 2-4, 8, and 10-56 are pending; claims 3-4 and 34-55 are withdrawn from examination per Applicants' election filed 5/21/2007.

Specification

2. Objection to the Specification because of minor informalities is withdrawn in view of amendment of the Specification filed 11/11/2008.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Rejection of claims 1, 2, 10-11, 13-33 and 56 under 35 U.S.C. § 103(a) as allegedly being obvious over Fletcher in view of Kemshead & Ugelstad, and Rudi *et al.* is **maintained** for reasons of record as elaborated below.

The claims are drawn to a method of cell separation that excludes specific binding pair interaction and includes magnetic microbeads. Further limitations of the basic method specifies the type of cell or virus (claims 2 and 27), the size of the beads (claim 10), modification or lack thereof of the microbead (claim 11), an additional washing step to remove undesirable constituents (claims 13, 31-32 and 56), an additional recovery step (claims 14 and 15), the nature of the sample

(claims 16-17 and 27-29), an additional step of recovering a biological material from the target (claims 18-19), the additional step of amplifying recovered oligonucleotide (claim 20), automation of the process (claim 21), absence of a precipitation step (claim 24) or poisonous agent (claim 25), ambient temperature during procedure (claim 26), pH range and presence of anticoagulant (claims 29-30).

Fletcher teaches a method of recovery of marine bacteria from cultures using the well-known property inherent in polystyrene to non-specifically affix proteins and cells to the surface. Of particular note is the teaching that the so-called panning method allows isolation and influence of model environmental proteins on viral attachment. Fletcher is used herein solely to establish that it has long been known that untreated polystyrene per se is useful for non-specific biological sample concentration resulting in viable organisms. Fletcher does not teach microbeads nor any of the limitations outlined above. Kemshead and Ugelstad teach the use of magnetic materials for medical applications. As one of the pioneer inventors of magnetic microbeads, Ugelstad is responsible for ensuring the size homogeneity of polymeric magnetic microbeads and inclusion of derivatized magnetic microbeads further useful in medically relevant treatment and diagnostic methods as well as usefulness in basic medical research. Kemshead and Ugelstad specifically teach separation methods using magnetic microbeads for a variety of cell types using both non-specific binding (see, for example, section II. Ways of generating magnetic cells) and specific binding

partners (see, for example, section III. Targeting 'magnetic material' to cells). Thus, the combination of Fletcher and Kemshead and Ugelstad teach that several types of cells can be separated and enriched from model environmental and clinical samples using magnetic polystyrene beads. Rudi, *et al.* teaches a method of using magnetic microbeads to sequentially separate bacteria from environmental samples and amplify separated DNA using the same magnetic microbeads.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Fletcher by substituting unmodified magnetic microbeads for polystyrene Petri dishes as taught by Kemshead and Ugelstad and/or Rudi, *et al.* The skilled artisan would have been motivated to do so because of the nonspecific adhesion of cells to polystyrene as taught by Fletcher and the rapidity of magnetic bead separation as taught by Kemshead and Ugelstad and/or Rudi, *et al.* especially when attempting isolation from rich sources of cells such as blood, cell cultures and/or dilute environmental sources. There would have been a reasonable expectation of success, given well-known absorptive properties of polystyrene, as taught by Fletcher and the general utility of magnetic bead separation methods as taught by many researchers especially including Kemshead and Ugelstad and/or Rudi, *et al.*

Applicant traverses the rejection by essentially arguing that the methods cited are not necessarily rapid (3-20 min), that Examiner only cited examples of non-

specific binding to one or perhaps two cell types, and one may conclude from the cited NPL that non-specific binding is undesirable.

Applicant's arguments have been fully considered but they are not persuasive. Regarding the slow attachment of Pseudomonas to polystyrene, Fletcher does not address the kinetics of cellular binding to polystyrene but rather reports conditions insuring maximum binding; Applicants' arguments relating to the time of the method are therefore unconvincing. Certain other claimed embodiments of the instantly claimed invention relate to conditions that are well known to effect cellular recovery rates and would be obvious to optimize by one of ordinary skill in the cell separation arts: Microbead size, washing steps, time of separation, temperature, source of sample, automation, use of certain disposable laboratory materials, pH, type and concentration of reagents, and the use of anticoagulants. Regarding Applicants' allegation that the Kemshead and Ugelstad and Rudi, *et al.* teach that non-specific binding is undesirable is unfounded; the use of antibody coated microbeads is simply more efficient than non-specific binding in cell separation technology. Regarding Applicants' allegation that one can not conclude that non-specific binding of *Ps. aeruginosa* attachment to polystyrene can not be generalized to other cell types is belied by the wealth of literature and experience of laboratory scientists as exemplified by a quick Google search which reveals that a wide variety of bacteria and other cell types bind to polystyrene (kindly see Vesper and Bauer; Maki, et al.; Genevaux, et al.; Trafny; Pringle and Fletcher). Cell types include *E. coli*, other *Ps.* species, *Staphylococci*,

Deleya marina sp., *Vibrio vulnificus*, Rhizobia and macrophages. Furthermore, carefully reading of Fletcher reveals that polystyrene generally binds proteins allowing the logical conclusion that pilliated bacteria, Gram negative bacteria, as well as many virions would non-specifically bind to polystyrene.

In sum, polystyrene is well known as an adherent agent to proteins, viruses, bacteria, and non-bacterial cells; polystyrene microbeads, depending on the cell type and bead size, would either bind adherent cells to their surfaces or decorate the cellular surfaces; and in either case, magnetization of the beads would expedite the recovery of bead/cell conjugates. Since each of the cited references teaches cellular concentration and/or separation, a skilled artisan would find it obvious to use magnetic, polystyrene bead to concentrate or separate cells whether to separate a known cell type of known polystyrene adherent phenotype or to sample environmental or clinical samples.

Allowable Subject Matter

4. Claim 8 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

5. No claims are allowed.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to STUART W. SNYDER whose telephone number is (571)272-9945. The examiner can normally be reached on 9:00 AM-5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mary E Mosher/
Primary Examiner, Art Unit 1648

Stuart W Snyder
Examiner
Art Unit 1648

sws